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Selective Synthesis and Characterization of Substituted 1,3,4-Thiadiazole/oxadiazole and 1,2,4-Triazole Heterocyclic Rings

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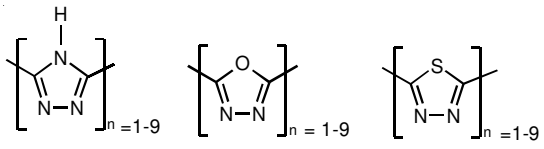
A new series of 5-(isomeric pyridyl)-1,3,4-thiadiazole **3(a-c)**/oxadiazole **6(a-c)** and 4-(4-fluoro phenyl)-5-(isomeric pyridyl)-1,2,4-triazole-3-thiol **4(a-c)**/3-methyl thiol **5(a-c)** derivatives were synthesized in excellent yield and under different conditions in order to obtain new compounds with potential significant biological activity. The starting compounds, thiosemicarbazides **2(a-c)**, were used as the key intermediates for the synthesis of heterocyclic compounds. The structures of the target compounds were characterized by IR, ^{1}H NMR and MS spectroscopy.

Key Words: Synthesis, 1,2,4-Triazole, 1,3,4-Oxadiazole, 1,3,4-Thiadiazole, Thiosemicarbazide.

INTRODUCTION

Azoles are important five membered heterocyclic rings containing at least one nitrogen atom. Triazole, oxa(thia)-diazoles have played a crucial part in the development in heterocyclic chemistry and also have extensive application in organic synthesis (Fig. 1).



(I) (II) (III)

Fig. 1. Structures of 1,2,4-triazole (I), 1,3,4-oxadiazole (II) and 1,3,4-thiadiazole (III)

1,2,4-Triazole, 1,3,4-oxadiazole and 1,3,4-thiadiazole derivatives show various biological, pharmaceutical, agro-chemical and agriculture activities. Also, the substituted of (I), (II) and (III) compounds have attracted significant interest in medical and pesticide chemistry and polymer and material science as anticancer[1-3], fungicidal and antimicrobial[4,5], anti-tubercular[6-9] and antiinflammatory[10,11] agents. Further, they also are significant in agrochemical industry as plant protecting materials[12], industrial chemistry and pharmacological activities such as anti convulsing[13-15], bactericides, pesticides, fungicides and photosensitive materials[14-16]. Several original activities as summarized Table-1.

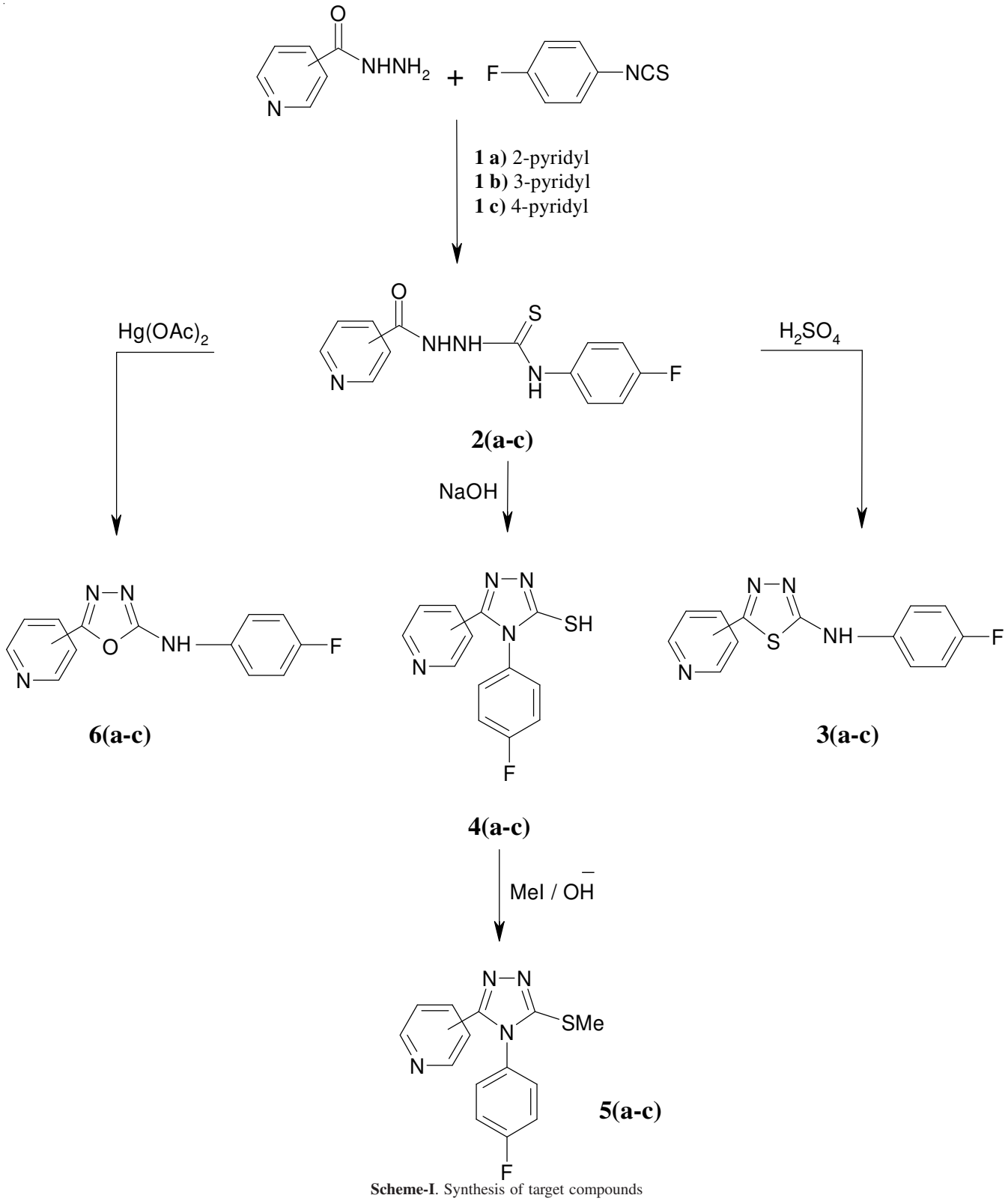
TABLE-1
BIOLOGICAL AND MEDICAL ACTIVITIES OF (I), (II) AND (III) DERIVATIVES ALONG WITH THE THIOSEMICARBAZIDE

Compounds	Activities
Triazole-derivatives	Fungicidal, Pesticides, Tranquilizers, Sedative, Antifungal, Analgesics, Anticonvulsant, Antidepressant, Anticancer, Lubricants.
Oxadiazole-derivatives	Antitubercular, Antifungal, Herbicidal, Antiparastic, Antimicrobial, Anti parkinsonian.
Thiadiazole - derivatives	Spasmolytic, Anti-inflammatory, Antibacterial, Plant growth regulative, Anti HIV-1, Anthelmintic.
Thiosemicar-bazide	Antibacterial, Antifungal, Herbicidal, Antitubercular, Anti acetyl cholinesterase.

Chemistry: The new oxadiazole and thiadiazole derivatives were prepared following the reaction sequences as depicted in **Scheme-I**. The starting material thiosemicarbazide was prepared by 4-fluoro phenyl isothiocyanate and isomeric pyridine carboxylic acid hydrazides **1(a-c)** in ethanol. The fourth and third carbon of azoles ring serves as main site for substitutions.

EXPERIMENTAL

All the recorded melting points were measured with an electrothermal digital melting point apparatus without uncorrected. The IR spectra were recorded on a spectrum UNICAM GALAXY series FTIR 5000 as potassium bromide (KBr) disks. The ^{1}H NMR spectra were recorded on a Bruker AV 300 MHz spectrophotometer in DMSO. Peak values are shown



Scheme-I. Synthesis of target compounds

in δ ppm. Mass spectra were taken using an EX1100 (Shimadzu, Kyoto, Japan) model GC MS-QP instrument. The course of reactions and purity of compounds was controlled by thin layer chromatography (TLC) on Merck 60 F254 silica gel-coated aluminum sheets and spots were detected by UV light (ethanol/*n*-hexane = 2/3). Chemical raw materials and solvents were purchased from MERCK.

Synthesis of 4-(4-fluoro phenyl)-1-(isomeric pyridol) thiosemicarbazides 2(a-c): Respective substituted pyridine carboxylic acid hydrazides **1(a-c)** (7.9 mmol) were dissolved in ethanol (96 %, 50-100 mL), depending upon the solubility of the compounds. The 4-fluoro phenyl isothiocyanate (7.9 mmol) was separately dissolved in ethanol (96 %, 10 mL) then the solution of the isothiocyanate was poured in to the

solution of hydrazide with continuous stirring. The reaction mixture was then refluxed. Each reaction required different times determined by TLC. After the completion of the reaction, the mixture cooled down to room temperature. As a result a white solid crystal appeared. The crude solid was then filtered off and recrystallized from appropriate solvent to yield the compounds.

2a: FT IR (KBr, ν_{max}, cm^{-1}): 3261 (NH), 3092 (Ar-H), 1657 (C=O), 1562-1427 (C=N, C=C), 1221 (C=S).

2b: FT IR (KBr, ν_{max}, cm^{-1}): 3246 (NH), 3174 (Ar-H), 1651 (C=O), 1500 (C=N, C=C), 1203 (C=S). ^{1}H NMR δ (DMSO-d_6): 7.14-7. 4 (m, 4H, Ar-H), 7.53-9.1 (m, 4H, Py-H), 9.84 (s, 1H, CSNH), 10.77 (s, 1H, CONH).

2c: FT IR (KBr, ν_{max}, cm^{-1}): 3209 (NH), 3100 (Ar-H), 1665 (C=O), 1420-1532 (C=N, C=C), 1230 (C=S). ^{1}H NMR δ (DMSO-d_6): 7.14 -7.39 (m, 4H, Ar-H), 7.83 -8.78 (m, 4H, Py-H), 9.86 (s, 1H, CSNH), 10.87 (s, 1H, CONH).

Synthesis of 2-(4-fluoroaniline) -5-(isomeric pyridyl)-1,3,4-thiadiazole 3(a-c): Each thiosemicarbazide **2(a-c)** (0.366 mmol) were dissolved in sulfuric acid (98 %, 5 mL) with continuous stirring. the compounds, the mixture was stirred further for different reaction time at room temperature. After the completion of the reaction, a mixture was cooled with crushed ice and then neutralized with ammonia (28 %). The resultant crude solid was filtered off and washed with water then dried in vaccum to give **3(a-c)**.

3a: FT IR (KBr, ν_{max}, cm^{-1}): 3209 (NH), 3053 (Ar-H), 1580 (C=N, C=C), ^{1}H NMR δ (DMSO-d_6): 7.18-7.21(d, 2H, Ar-H), 7.49-7.68 (d, 2H, Ar-H), 7.24(s, 1H, Py-H), 7.97 (s, 1H, Py-H), 8.12-8.15(d, 1H, Py-H), 8.64(s, 1H, Py-H), 10.64 (s, 1H, NH).

3b : FT IR (KBr, ν_{max}, cm^{-1}): 3143 (NH), 3043 (Ar-H), 1506 (C=N, C=C). ^{1}H NMR δ (DMSO-d_6): 7.2-7. 26 (t, 2H, Ar-H), 7.67-7.72 (q, 2H, Ar-H), 7.53-7. 58 (q, 1H, Py -H), 8.24-8.27 (d, 1H, Py-H), 8.67-8.69 (t, 1H, Py-H), 9.04-9.05 (d, 1H, Py-H), 10.34 (s, 1H, NH). MS. m/z (%): 272(M^+, 100), 271 (60), 168 (85), 119 (75), 104 (35), 95 (70), 78 (60).

3c : FT IR (KBr, ν_{max}, cm^{-1}): 3209(NH), 3055 (Ar-H), 1584 (C=N, C=C). ^{1}H NMR δ (DMSO-d_6): 7.23(s, 2H, Ar-H), 7.81 (s, 2H, Ar-H), 7.82-7.83 (d, 2H, Py-H), 8.69-8.71 (d, 2H, Py-H), 10.76 (s, 1H, NH).

Synthesis of 4-(4-fluoro phenyl)-5-(isomeric pyridyl)-1,2,4- triazole-3-thiole 4(a-c): Solid thiosemicarbazides **2(a-c)** (2.1 mmol) were added portion wise to 20 mL of 2N sodium hydroxide solution. The reaction was refluxed and monitored by TLC. After the completion of the reaction, the mixture was allowed to cool down and then it was acidified with 2N hydrochloric acid to reach PH = 4. The crude products obtained upon cooling were filtered off and washed with water. In addition, to obtain purified compounds, the products were also dissolved in concentrated NaOH and then the HCl was added drop wise to pH = 7.

4a: FT IR (KBr, ν_{max}, cm^{-1}): 3109 (Ar-H), 2818 (SH), 1540-1514 (C=N, C=C). ^{1}H NMR δ(DMSO-d_6): 7.25-7.42 (m, 4H, Ar-H), 7.36-7.38 (d, 1H, Py-H), 7.84-7.94 (m, 2H, Py-H), 8.33-8.35 (d, 1H, Py-H), 14.26 (s, 1H, SH).

4b : FT IR (KBr, ν_{max}, cm^{-1}): 3068(Ar-H), 2706(SH), 1552-1450 (C=N, C=C). ^{1}H NMR δ (DMSO-d_6): 7.32-7.51 (m, 4H, Ar-H), 7. 4-7.43 (m, 1H, Py-H), 7.64-7.68 (d, 1H, Py-H), 8.52-8.53 (d, 2H, Py-H), 8.58-8.61 (q, 1H, Py-H), 14.28 (s, 1H, SH). MS. m/z (%): 272(M^+, 100), 271 (90), 239(10), 213(30), 135(20), 95(65).

4c : FT IR (KBr, ν_{max}, cm^{-1}): 3057 (Ar-H), 2731 (SH), 1590-1552 (C=N, C=C). ^{1}H NMR δ (DMSO-d_6): 7.24-7.41 (m, 4H, Ar-H), 7.4 -8.6 (m, 4H, Py-H), 14.37(s, 1H, SH).

Synthesis of 3-(methyl thio)-4-(4-fluoro phenyl)-5-(isomeric pyridyl)-1,2,4-tri azole 5(a-c): A mixture of suitable substituted triazole-3 thiole (0.034 mmol), corresponding methyl iodide (0.034 mmol) in ethanolic alkali (0.019 g KOH in 20 mL EtOH 95%):

Method A: The reaction mixture was refluxed and completion of reaction checked by using TLC. The reaction conditions were established experimentally. On the cooling of the reaction mixture, the crude precipitate was collected, washed with ether and finally recrystallized.

Method B: The reaction mixture was transferred to an isolated volumetric flask and then was placed in ultrasonic bath. The completion of reaction checked by using TLC. On the cooling of the reaction mixture, the solid compounds were washed with ether and then recrystallized.

5a: FT IR (KBr, ν_{max}, cm^{-1}): 3078 (Ar-H), 2933 (R-H), 1553-1510 (C=N, C=C). ^{1}H NMR δ (DMSO-d_6): 2.63(s, 3H, CH3), 7.31 -7.48 (m, 4H, Ar-H), 7.43 (d, 1H, Py-H), 7.91-7.92 (d, 1H, Py-H), 8.0-8.03 (d, 1H, Py-H), 8.3-8.32 (d, 1H, Py-H). MS. m/z (%): 287(M^+, 80), 271(20), 239(17), 212(25), 191(15), 95(65), 78(80).

5b: FT IR (KBr, ν_{max}, cm^{-1}): 3015 (Ar-H), 2928 (R-H), 1536 (C=N, C=C). ^{1}H NMR δ (DMSO-d_6): 2.63 (s, 3H, CH3), 7.39-7.6 (m, 4H, Ar-H), 7.45 (s, 1H, Py-H), 7.69-7.72 (q, 1H, Py-H), 8.57-8.59 (d, 2H,Py-H).

5c: FT IR (KBr, ν_{max}, cm^{-1}): 3053 (Ar-H), 2935 (R-H), 1506-1442 (C=N, C=C). ^{1}H NMR δ (DMSO-d_6): 2.63 (s, 3H, CH3), 7.3-7.46 (m, 4H, Ar-H), 7.6-8.58 (m, 4H, Py-H).

Synthesis of 2-(4-fluoroaniline)-5-(isomeric pyridyl)-1,3,4-oxadiazole 6(a-c): Each thiosemicarbazide **2(a-c)** (0.0264 mmol) was dissolved in ethanol (96 %, 50-80 mL), depending upon the solubility of the compounds. Then $Hg(OAc)_2$ (0.0264 mmol) was added portion wise to flask and the reaction mixture was refluxed. Over time, the contents were changed colour and were black. The reaction time was monitored by TLC in normal hexane and methanol (3:2) solution. After the reaction completed, the mixture was cooled down to room temperature and the white product obtained **6(a-c)** was separated by filtration.

6a: FT IR (KBr, ν_{max}, cm^{-1}): 3119 (NH), 3090 (Ar-H), 1597-1566 (C=N, C=C). ^{1}H NMR δ (DMSO-d_6): 7.2-7.26 (t, 2H, Ar-H), 7.61-7.66 (q, 2H, Ar-H), 7.79 -7.81 (t, 2H,Py-H), 8.77 -8.79 (t, 2H,Py-H), 10.7-10.9(br s, 1H, NH). MS. m/z (%): 256 (M^+,100), 146 (45), 110 (50), 95 (25), 78 (95), 51 (80).

6b: FT IR(KBr, ν_{max}, cm^{-1}): 3110 (NH), 3058 (Ar-H), 1597-1566 (C=N, C=C). ^{1}H NMR δ (DMSO-d_6): 7.2-7.26 (t, 2H, Ar-H), 7.6-7.65 (m, 2H, Ar-H), 7.66 (s, 1H, Py-H), 8.23 -8.27 (m, 1H, Py-H), 8.74-8.76 (q, 1H, Py-H), 9.06-9.07 (d, 1H, Py-H), 10.7-10.9 (br s, 1H, NH).

6c: FT IR (KBr, ν_{max}, cm^{-1}): 3113 (NH), 3095 (Ar-H), 1595-1573 (C=N, C=C). ^{1}H NMR δ (DMSO-d_6): 7.2-7.26 (t, 2H, Ar-H), 7.61-7.66 (q, 2H, Ar-H), 7.8-7.81 (q, 2H, Py-H), 8.78-8.8 (t, 2H, Py-H), 10.7-11.1 (br s, 1H, NH).

TABLE-2
PHYSICAL DATA OF TARGET COMPOUNDS FROM **2a** TO **6c** (R=2,3,4-PYRIDYL), (R' =FLUORO PHENYL)

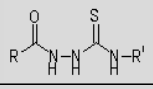
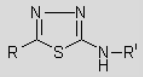
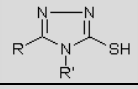
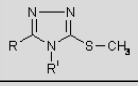
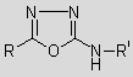
No.	Molecule	Formula	Colour	Yield (%)	m.p. (°C)
2a		$C_{13}H_{11}N_4OSF$	White	90	191-192
2b		$C_{13}H_{11}N_4OSF$	White	82	194-195
2c		$C_{13}H_{11}N_4OSF$	White	97	197-198
3a		$C_{13}H_9N_4FS$	Light Yellow	83	228-230
3b		$C_{13}H_9N_4FS$	Light Yellow	72	271-272
3c		$C_{13}H_9N_4FS$	Light Yellow	91	176-177
4a		$C_{13}H_9N_4FS$	White	93	243-245
4b		$C_{13}H_9N_4FS$	White	90	277-279
4c		$C_{13}H_9N_4FS$	White	97	272-273
5a		$C_{14}H_{11}N_4OS$	White	85	152-154
5b		$C_{14}H_{11}N_4OS$	White	83	144-145
5c		$C_{14}H_{11}N_4OS$	White	92	189-190
6a		$C_{13}H_9N_4FO$	White	80	195-197
6b		$C_{13}H_9N_4FO$	White	70	256-257
6c		$C_{13}H_9N_4FO$	White	85	243-244

TABLE-3
^{1}H-NMR AND IR DATA OF COMPOUNDS **3(a-c)**, **4(a-c)** AND **6(a-c)**

No.	^{1}H- NMR: δ(DMSO-d_6)			IR (KBr): cm^{-1}		
	(4H, Ar-H)	(4H, Py-H)	(1H, s, NH)	$\nu_{(N-H)}$	$\nu_{(Ar-H)}$	$\nu_{(C=N, C=C)}$
3a	7.18-7.49	7.68-8.15	10.64	3209	3053	1580
3b	7.2-7.72	7.6-9.05	10.34	3143	3043	1506
3c	7.23-7.81	7.82-8.71	10.76	3209	3055	1585
4a	7.26-7.4	7.42-8.35	14.26*	2818*	3109	1514-1540
4b	7.32-7.5	7.6-8.6	14.28*	2706*	3068	1450-1552
4c	7.23-7.41	7.48-8.6	14.37*	2731*	3057	1552-1590
6a	7.2-7.6	7.8-8.7	10.7-10.9	3119	3090	1566-1597
6b	7.2-7.6	7.64-9.06	10.7-10.9	3110	3058	1566-1597
6c	7.2-7.6	7.7-8.7	10.7-11.1	3113	3095	1573-1595

*^{1}H NMR (1H, s, SH) and $\nu_{(S-H)}$ respectively

RESULTS AND DISCUSSION

Our earlier study involved synthesis of heterocyclic compounds containing in their bearing isomeric pyridine and azoles structures. In consideration of this type of compounds and in continuation of our interest in the synthesis of biologically active hetrocycles, the aim of the present work was to develop simple and efficient procedures for the preparation of new 1,2,4-triazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole derivatives bearing substituted pyridine moiety. In the present work, various thiosemicarbazides were synthesized by condensing 4-fluoro phenyl isothiocyanate with isomeric pyridine carboxylic acid hydrazides **2(a-c)** that were used as the key intermediates for the synthesis of heterocyclic compounds. The majority of obtained compounds are new and spectral and elemental analyses have not been reported in the literature as yet.

The structure of products **2(a-c), 3(a-c), 4(a-c), 5(a-c)** and **6(a-c)** were elucidated by the ^{1}H NMR spectra. These data suggest unsymmetrical structure of products, which means that the substitution occurred at the diazole rings. Chemical shift values were mentioned in δ ppm. The elemental analysis, ^{1}H NMR and IR data of compounds are respectively listed in Tables 2 and 3.

The infrared spectra of compounds **2(a-c)** exhibited a characteristic strong absorption at 1230-1203 cm^{-1} attributable to the (C=S) of the thiourea residue. The carbonyl absorption in these compounds was observed at 1665-1651 cm^{-1}.

Each isomeric thiosemicarbazides **2(a-c)** in sulfuric acid afforded corresponding substituted 1,3,4-thiadiazole **3(a-c)** respectively.

In the infrared spectra of compounds **3(a-c)** the absence of signals in the region 1665-1651 cm^{-1} and 1230-1203 cm^{-1} established the lack of (C=O) and (C=S) group. ^{1}H NMR and mass spectral data of the compounds (MS. m/z (%) : 272 (M^+, 100), 168(85), 119 (75) supported this.

The dehydrative cyclization of **2(a-c)** in sodium hydroxide afforded corresponding substituted 1,2,4-triazole **4(a-c)** respectively. In the infrared spectra of compounds **4(a-c)** the absence of signals in the region 1665-1651 cm^{-1} established the lack of a (C=O) group. ^{1}H NMR and mass spectral data of the compounds (MS. m/z (%) : 272 (M^+, 100), 271 (90), 239 (10), 213 (30) supported this. In the ^{1}H NMR data of compounds **4(a-c)** a single peak in the region 14.26-14.37 ppm was observed due to (S-H) proton.

The refluxing of compounds **4(a-c)** with methyl iodide in alkaline ethanol yielded methylthio derivatives of 1,2,4-triazole and the absence of signals in the region 1203-1230 cm^{-1} and above 3200 cm^{-1} in IR spectral data established the absence of (C=S) and (NH) respectively. ^{1}H NMR and mass spectral data of the compounds (MS m/z (%) : 287(M^+, 80), 271(20), 239 (17)) supported this. In the ^{1}H NMR data of compounds **5(a-c)** the absence of signals in the region 14.26-14.37 ppm established the lack of a(S-H) proton.

$Hg(OAc)_2$ was added to each isomeric thiosemicarbazides **2(a-c)** in ethanol and reaction afforded corresponding substituted 1,3,4-oxadiazole **6(a-c)** respectively. In the infrared spectra of compounds **6(a-c)** the absence of signals in the region 1665-1651 cm^{-1} and 1230-1203 cm^{-1} established the lack of (C=O) and (C=S) group. ^1H NMR and mass spectral data (MS. m/z (%): 256 (M^+, 100), 146 (45), 110 (50), 95 (25), 78 (75) of the compounds supported this.

Conclusion

From the present study, it can be concluded that the synthesized oxa(thia)diazole derivatives can be potentially be developed into useful biological agents that can prompt future researcher to synthesize a series of these compounds containing wide varieties of substituent with the aim of obtaining some novel heterocyclic systems with enhanced medical and biological properties. The quantum chemical investigation of the presented compounds will be reported in the future publications.

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